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(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

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14 April 1994 (14.04.94)

(54) Title: MEDICAMENTS FOR THE TREATMENT OF VISCERAL PAIN AND MIGRAINE

(57) Abstract

The invention relates to the use of those 5-HT_3 receptor antagonists, which are active in the Rat Model of Colo-rectal Distension at a dose determined as the dose at which 5-HT_3 receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model, in the treatment of visceral pain, such as the pain symptoms of IBS, and also migraine.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB93/01377

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please see attached sheet ../..

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

For further information please see form PCT/ISA/206 sent to you 19.01.1994.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-6 (partially),8

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/01377

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/00 A 61 K 31/165 A 61 K 31/435
A 61 K 31/46

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X,D	GUT vol. 31, no. 10 , 1990 page A1174 A. PRIOR ET AL. 'REDUCTION OF RECTAL SENSITIVITY AND POST-PRANDIAL MOTILITY BY GRANISETRON, A 5-HT3 RECEPTOR ANTAGONIST, IN PATIENTS WITH IRRITABLE BOWEL SYNDROME (IBS)' cited in the application see abstract ---	1-6,8
A	R.BERKOW, ED. 'THE MERCK MANUAL OF DIAGNOSIS AND THERAPY, 15TH EDITION' 1987 , MERCK & CO. , RAHWAY, N.J. see page 808 - page 810 ---	1-6,8
X,P	WO,A,9211259 (BEECHAM GROUP PLC) 9 July 1992 see page 10, line 30 - line 31 see page 11, line 6 see page 13, line 31 - page 14, line 4 --- -/-	1-6,8

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29-11-1993	18. 03. 94
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	THEUNS

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X,P	WO,A,9214733 (SMITH-KLINE BEECHAM P.L.C.) 3 September 1992 see page 15, line 10 - line 11 see page 15, line 22 see page 18, line 8 - line 18 ---	1-6,8
X	EP,A,0289170 (BEECHAM GROUP PLC) 2 November 1988 see page 9, line 3 - line 4 see page 9, line 8 - line 9 see page 9, line 54 - page 10, line 1 ---	1-6,8
X,P	WO,A,9212149 (SMITH-KLINE BEECHAM PLC) 23 July 1992 see page 11, line 28 - line 29 see page 12, line 5 see page 14, line 29 - page 15, line 2 ---	1-6,8
X	ALIMENT.PHARMACOL.THER. vol. 6, no. 3 , June 1992 pages 273 - 289 N.J.TALLEY 'REVIEW ARTICLE: 5-HYDROXYTRYPTAMINE AGONISTA AND ANTAGONISTS IN THE MODULATION OF GASTROINTESTINAL MOTILITY AND SENSATION: CLIMICAL IMPLICATIONS' see summary see page 278, last line - page 279, line 4 see page 280. climical implications - page 282, first paragraph ---	1-6,8
X	EP,A,0387431 (BEECHAM GROUP PLC) 19 September 1990 see page 8, line 40 - line 41 see page 8, line 43 see page 9, line 33 - line 38 ---	1-6,8
X	WO,A,9205174 (BEECHAM GROUP PLC) 2 April 1992 see page 17, line 2 - line 3 see page 17, line 14 see page 20, line 5 - line 15 ---	1-6,8
X	WO,A,8909217 (BEECHAM GROUP PLC) 5 October 1989 see page 11, line 5 - line 6 see page 11, line 10 see page 14, line 1 - line 13 ---	1-6,8
X	WO,A,9101316 (BEECHAM GROUP PLC) 7 February 1991 see page 6, line 1 - line 2 see page 6, line 6 - line 7 see page 9, line 13 - line 23 ---	1-6,8
X,P	EP,A,0504679 (G.D.SEARLE & CO.) 23 September 1992 see page 4, line 58 see page 5, line 1 see page 36, line 23 - line 29 --- -/-	1-6,8

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	EP,A,0315316 (BEECHAM GROUP PLC) 10 May 1989 see page 8, line 40 see page 8, line 42 - line 43 see page 9, line 33 - line 38	1-6,8
X	EP,A,0315390 (BEECHAM GROUP PLC) 10 May 1989 see page 9, line 48 - line 51 see page 10, line 44 - line 49	1-6,8
X	EP,A,0287196 (BEECHAM GROUP PLC) 19 October 1988 see page 8, line 47 - line 51 see page 9, line 42 - line 47	1-6,8
X,P	US,A,5137893 (G.D.SEARLE & CO.) 11 August 1992 see column 3, line 13 - line 14 see column 15, line 13 - line 19	1-6,8
X	EP,A,0272876 (GLAXO GROUP LIMITED) 29 June 1988 see page 2, line 53 - line 54	1-6,8
X	EP,A,0364274 (GLAXO GROUP LIMITED) 18 April 1990 see page 4, line 25 see page 5, line 37 - line 41	1-6,8
X	EP,A,0381422 (YAMANOUCHI PHARMACEUTICAL CO. LTD.) 8 August 1990 see page 6, line 21 - line 22 see page 6, line 31 - line 34	1-6,8
X	EP,A,0377967 (BEECHAM GROUP PLC) 18 July 1990 see page 8, line 5 - line 6 see page 8, line 11 see page 8, line 57 - page 9, line 4	1-6,8
X	EP,A,0376624 (YAMANOUCHI PHARMACEUTICAL CO. LTD.) 4 July 1990 see page 4, line 53 - line 54 see page 5, line 55 - line 59	1-6,8
X	EP,A,0189002 (SANDOZ AG) 30 July 1986 see page 19, line 17 see page 20, line 11 - line 22	1-6,8

-/-

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	US,A,5126343 (ZABROWSKI ET AL.) 30 June 1992 see column 11, paragraph 2 -paragraph 3 ---	1-6,8
X	WO,A,9107402 (PFIZER INC.) 30 May 1991 see page 1, line 12 - line 14 ---	1-6,8
X	EP,A,0317088 (GLAXO GROUP LIMITED) 24 May 1989 see page 5, line 44 see page 6, line 52 - line 57 ---	1-6,8
X	GB,A,2192885 (GLAXO GROUP LIMITED) 27 January 1988 see page 2, line 38 see page 3, line 36 - line 40 ---	1-6,8
X	EP,A,0357416 (GLAXO GROUP LIMITED) 7 March 1990 see page 3, line 1 ---	1-6,8
X	EP,A,0347229 (GLAXO GROUP LIMITED) 20 December 1989 see page 4, line 50 see page 5, line 51 - line 55 ---	1-6,8
X	EP,A,0356098 (GLAXO GROUP LIMITED) 28 February 1990 see page 5, line 5 see page 6, line 16 - line 20 ---	1-6,8
X	EP,A,0351385 (INSTITUTO DE ANGELI S.P.A.) 17 January 1990 see page 6, line 55 - line 56 ---	1-6,8
X	EP,A,0361317 (FUJISAWA PHARMACEUTICAL CO.,,LTD.) 4 April 1990 see page 13, line 29 - line 33 see page 12, line 4 see page 12, line 7 ---	1-6,8
X	EP,A,0358903 (DAINIPPON PHARMACEUTICAL CO., LTD.) 21 March 1990 see page 17, line 22 - line 39 ---	1-6,8
X	EP,A,0345956 (GLAXO GROUP LIMITED) 13 December 1989 see page 5, line 9 see page 6, line 18 - line 23 --- -/-	1-6,8

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X,P	EP,A,0518767 (MERRELL DOW PHARMACEUTICALS INC.) 16 December 1992 see page 2, line 4 see page 2, line 7 see page 11, line 27 - line 30 see page 14, line 26 - line 30 ---	1-6,8
X	EP,A,0454121 (G.D.SEARLE & CO.) 30 October 1991 see page 3, line 31 see page 3, line 34 ---	1-6,8
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X	EP,A,0419397 (A/S FERROSAN) 27 March 1991 see page 4, line 22 see claim 5 ---	1-6,8
X	EP,A,0417746 (G.D.SEARLE & CO.) 20 March 1991 see page 11, line 55 - line 56 see page 12, line 2 ---	1-6,8
X	EP,A,0385722 (GLAXO GROUP LIMITED) 5 September 1990 see page 4, line 44 see page 5, line 53 - line 58 ---	1-6,8
X	EP,A,0266899 (GLAXO GROUP LIMITED) 11 May 1988 see page 4, line 54 see page 5, line 54 - line 58 ---	1-6,8
X	EP,A,0254584 (BEECHAM GROUP PLC) 27 January 1988 see page 14, line 1 see page 14, line 13 see page 17, line 1 - line 13 ---	1-6,8
X	WO,A,9112254 (NOVO NORDISK A/S) 22 August 1991 see page 4, line 9 - line 11 see claim 5 ---	1-6,8
X	EP,A,0336759 (GLAXO GROUP LIMITED) 11 October 1989 see page 4, line 24 see page 5, line 25 - line 29 --- -/-	1-6,8

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
E	EP,A,0554794 (EISAI CO., LTD.) 11 August 1993 see page 30, line 50 - line 55 see page 31, line 7 - line 13 ---	1-6,8
X,D	EP,A,0450757 (GLAXO GROUP LIMITED) 9 October 1991 cited in the application see page 2, line 34 - line 35 see page 3, line 2 - line 3 ---	1-6,8
X	EP,A,0377967 (BEECHAM GROUP PLC) 18 July 1990 see page 8, line 4 - line 11 see page 8, line 57 - page 9, line 4 ---	1-6,8
X,D	EP,A,0279512 (BEECHAM GROUP PLC) 24 August 1988 cited in the application see the whole document -----	1-6,8

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

MEANINGFUL SEARCH NOT POSSIBLE OR INCOMPLETE SEARCH

1. The subject matter of claim 7 violates the requirements of Art. 6 and Rule 6.2 PCT. For that reason, no search was performed for the subject matter of claim 7.
2. In view of the definition of compounds by means of their pharmacological profile rather than by structural parameters, the search (within the framework of the first subject of the lack of unity objection) was limited to such compound(s) for which a structural identification was possible (Art. 6 PCT; Guidelines B-II, 7, last sentence, and B-III, 3.7).
3. The attention of the Applicant is drawn to the fact that the ISA is not in the position to perform experiments in order to identify known compounds having the presently claimed pharmacological utility as 5-HT_3 antagonists, or to assess the doses referred to in the claims. As a consequence it may very well be that relevant prior art has not been retrieved (Art. 6 PCT).
4. Although claims 1-2, 4-6 and 8-9 are directed to a method of treatment of the human/animal body (Rule 39.1(iv) PCT) the search for the first subject has been based on the alleged effects of the compound/composition.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9301377 SA 76526

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9301377 SA 76526

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(54) Title: MEDICAMENTS FOR THE TREATMENT OF VISCERAL PAIN AND MIGRAINE

(57) Abstract

The invention relates to the use of those 5-HT_3 receptor antagonists, which are active in the Rat Model of Colo-rectal Distension at a dose determined as the dose at which 5-HT_3 receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model, in the treatment of visceral pain, such as the pain symptoms of IBS, and also migraine.

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MEDICAMENTS FOR THE TREATMENT OF VISCERAL PAIN AND MIGRAINE

This invention relates to the use of certain compounds which are 5-HT_3 receptor antagonists as visceral analgesics.

EP-A-279512 (Beecham Group p.l.c.) describes the use of certain 5-HT_3 receptor antagonists, including granisetron (KYTRIL) in the treatment of visceral pain.

Visceral pain is a symptom of irritable bowel syndrome (IBS) and granisetron has been found to desensitise the rectum in IBS patients as shown by double-blind placebo-controlled studies, at doses of 120 µg/kg and 50 µg/kg, 120 µg/kg being most effective. (Prior and Read, 1990; Gut 31 (10) A1174).

Granisetron has been found to be active in an animal model of rectal sensitivity to distension (see method described hereafter).

5-HT_3 receptor antagonists which have the same effect as granisetron in this model, include zatosetron (Lilly) and metoclopramide.

The invention therefore relates to the use of those 5-HT_3 receptor antagonists, which are active in the animal model at a dose determined as the dose at which 5-HT_3 receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model, in the treatment of visceral pain, such as the pain symptoms of IBS, and also migraine.

Preferred compounds are active at a lower dose than the 5-HT_3 receptor antagonist dose. Compounds which are approved or under clinical investigation are active at a similar dosage level to that which is used for antiemetic use.

Suitable modes of administration, formulations, etc. are as described in EP-A-279512.

5-HT_3 receptor antagonists which should be considered for this invention include those specifically and generically disclosed and referenced in EP-A-450757 (Glaxo Group Limited).

Rat Model of Colo-rectal Distension

A 6-7 cm latex balloon was inserted intra-anally into male Wistar rats (250-650g) under halothane anaesthesia; the balloon catheter was taped to the tail. After recovery the animals were allowed unrestricted movement and were dosed with either vehicle (saline) or 5-hydroxytryptophan (5-HTP 10mgkg^{-1} subcutaneously). At 5 min post-dose a ramp inflation of the colo-rectal balloon was carried out for approximately 10-30s until the visceromotor threshold (abdominal muscle contraction) was observed; the stimulus was then immediately removed and threshold pressure noted. This inflation procedure was repeated at 5 min intervals. 5-HT$_3$ receptor antagonists or saline were dosed subcutaneously after 3 stable responses were achieved and within 45 min of dosing 5-HTP or vehicle. The visceromotor threshold values were then recorded for a further 30 min. A similar model was described by Ness & Gebhart (1988, Brain Res. 450, 153-169). Maximum percentage changes (within the 30 min post-dose period) in distension pressure were compared with the mean of the pre-dose recordings. Saline control values were then assigned the value of 1.00 and drug induced changes compared directly.

Saline vehicle had no effect on the visceromotor threshold, whilst the dose of 5-HTP caused a reduction in the distension pressure required to elicit a response to the noxious stimulus (mean reduction of 30.7 $\pm$ 4.4%). Thus, by using a dose of 5-HTP that did not cause dramatic increases in gut secretion, the rat colo-rectum could be sensitised to colo-rectal distension.

Addition of saline after a pre-dose of 5-HTP had no effect on the decrease in threshold pressure caused by 5-HTP. By comparison, it was found that some, BUT NOT ALL, 5-HT$_3$ receptor antagonists when administered after 5-HTP dose dependently raised the visceromotor threshold above pre-dose values, thereby displaying a reduction in the sensitivity of the sensitized colo-rectum and producing analgesia to noxious levels of visceral distension. The Table shows the differences between selected 5-HT$_3$ receptor antagonists. Note that those antagonists that are active as visceral analgesics all display bell-shaped dose effect curves.

COMPOUND	DOSE	INDEX	SEM
	$\mu g/kg^{-1}$		
saline	-	1.00	0.27
5-HTP	10 000	-1.63	0.23
granisetron	1	2.17	0.40
	10	4.18	0.59
	100	2.86	0.66
	1000	2.17	0.37
	10 000	2.00	0.69
tropisetron	10	1.31	0.33
	100	1.77	0.73
metoclopramide	1	1.88	0.35
	10	2.69	0.43
	100	2.15	0.65
BRL 46470	1	0.46	0.38
	10	1.50	0.32
	100	0.02	0.28
	1000	0.55	0.39
E5*	1	2.54	0.87
	10	4.31	0.60
	100	1.79	0.56
ondansetron	10	1.03	0.15
	100	0.94	0.20
	1000	0.44	0.24
	10 000	1.61	0.49
zatosetron	1	2.73	0.77
	10	3.55	0.44
	100	2.66	0.55

*Example 5 of EP-A-377967

Thus it can be seen that granisetron, E5 and zatosetron are visceral analgesics (increasing threshold values above control by > 4-fold) falling within the invention.

Intrathecal administration of granisetron (100mg) also showed good analgesic activity suggesting that a site of action, of those 5-HT_3 receptor antagonists that are visceral analgesics, may be in the spinal cord. Furthermore, recent evidence from neonatally capsaicin treated rats, where there is c-fibre deafferentation, suggests the presence of these 5-HT_3 receptors on primary afferent fibres or a role for these receptors in sensory processing mediated by capsaicin sensitive afferents.

Claims

1. A method for the treatment and/or prophylaxis of visceral pain, in mammals, including humans, which method comprises administering to the mammal in need of such treatment and/or prophylaxis, an effective and/or prophylactic amount of a 5-HT_3 receptor antagonist, which is active in the animal model at a dose determined as the dose at which 5-HT_3 receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model.

2. The use of those 5-HT_3 receptor antagonists, which are active in the animal model at a dose determined as the dose at which 5-HT_3 receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model, in the treatment of visceral pain.

3. A pharmaceutical composition for use in the treatment and/or prophylaxis of visceral pain, which comprises a 5-HT_3 receptor antagonist, which is active in the animal model at a dose determined as the dose at which 5-HT_3 receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model, and a pharmaceutically acceptable carrier.

4. A method, use or composition according to claim 1, 2 or 3 wherein the compound is active at a lower dose than the 5-HT_3 receptor antagonist dose.

5. A method, use or composition according to claim 4 for the treatment of the pain symptoms of IBS.

6. A method, use or composition according to claim 5 for the treatment of also migraine.

7. A method, use or composition according to claim 1, 2 or 3 wherein the 5-HT_3 receptor antagonist is selected from those specifically and generically disclosed and referenced in EP-A-450757 (Glaxo Group Limited).

8. A method, use or composition according to claim 1, 2 or 3 wherein the 5-HT_3 receptor antagonist is granisetron.

9. A method, use or composition according to claim 1, 2 or 3 wherein the 5-HT_3 receptor antagonist is zatosetron (Lilly) or metoclopramide.